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(71) *Sökande* / *Applicant (s)* — *Sahltech i Göteborg AB, Göteborg SE*

(21) *Patentansökningsnummer* / *Patent application number* — *9904424-0*

(86) *Ingivningsdatum* / *Date of filing* — *1999-12-03*

(30) *Prioritet begärd från* — *1999-07-13 SE 9902680-9*

Stockholm, 2000-08-15

För Patent- och registreringsverket
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Vår referens
SE-2006205

USE OF INTERLEUKIN-6 IN COMBINATION WITH LEPTIN IN TREATMENT OF OBESITY AND DISTURBANCES OF BLOOD FATS

Summary

The present invention relates the use of interleukin-6 in combination with leptin in treatment of obesity and disturbances of blood fats.

Leptin plays a crucial role in the regulation of body weight and complete lack of leptin leads to severe obesity. However, most obese humans generally have high rather than low levels of leptin, and do not respond well to leptin treatment. This may be due to postreceptor leptin resistance at the hypothalamic level. Alternatively leptin might need cofactors for its action. We have recently found that absence of the pro-inflammatory cytokine interleukin-6 (IL-6) in knockout mice induces "middle age onset" obesity. In the present study we examined the effect of leptin treatment on food intake and body weight in 15-month-old IL-6 knockout (IL-6 $^{-/-}$) and wild-type mice. The body weights of the IL-6 $^{-/-}$ mice in the present study were increased with 17% compared to wild-type mice whereas no significant difference in plasma leptin levels was seen between old IL-6 $^{-/-}$ and wild-type mice. Treatment with leptin (120 µg/day and 240 µg/day) intraperitoneally twice daily for 3 days, significantly decreased food intake in the wild-type mice, but not in the IL-6 $^{-/-}$ mice. The leptin treatment also decreased body weight to a larger extent in wild-type than in IL-6 $^{-/-}$ mice. These findings indicate that presence of endogenous IL-6 is of importance for normal leptin responsiveness.

Introduction

Understanding obesity

Severe and moderate obesity is coupled to increased health risk since it is associated with diseases such as diabetes, hypertension and heart disease, whose incidence increases with body-mass index (BMI, body mass in kg/square of height in meters). A study based on information on 18-year-old Swedish military conscripts show a 1.4-fold increase in prevalence of overweight (BMI >25) and a 1.7-fold increase in obesity (BMI >30) from the year 1971 to 1993 (Rasmussen F, Johansson M and Hansen HO, 1999). The general opinion that obesity is largely the result of a lack of willpower is unsatisfactory. Intense research efforts are therefore made to reveal the genetic and environmental factors of importance for development of obesity (Friedman JM and Halaas JL, 1998).

Leptin

Five years ago the *ob* gene was cloned and characterised (Zhang Y *et al.*., 1994) and it was demonstrated that its protein product leptin reverses the severe obesity and diabetes seen in *ob/ob* mice. The 16 kDa protein leptin is almost only produced in white adipocytes from which leptin is then released to circulation. Leptin production by fat and plasma leptin levels is highly correlated with adipose tissue mass (Flier JS, 1997). Leptin acts through specific receptors in the hypothalamus to create a feedback loop for body weight regulation. Therefore, the pathophysiology of obesity was assumed to be partly endocrine. Leptin does not rise significantly after a meal and does not result in the termination of a meal. Instead leptin appears largely to exert long-term effects on food consumption and energy expenditure (Friedman JM and Halaas JL, 1998).

Leptin as a starvation signal

Obese (*ob*) mice which lack leptin show many of the abnormalities seen in starved animals, including hyperphagia, decreased body temperature, decreased energy expenditure, decreased immune function, and infertility. Leptin replacement corrects all of these abnormalities which implying that *ob* mice live in a state of "perceived starvation" due to lack of leptin and that the biological response in the presence of food leads to obesity. These observations led to speculation that leptin's main physiological role is to signal nutritional status during periods of food deprivation (Friedman JM and Halaas JL, 1998).

The leptin receptors

The leptin receptor (Ob-R) is normally expressed at high levels in hypothalamic neurons and in other cell types, including T cells and vascular endothelial cells. *In situ* hybridisation was used to identify the hypothalamic arcuate nucleus, dorsomedial hypothalamic nucleus (DMH), paraventricular nucleus (PVN), ventromedial hypothalamic nucleus (VMH) and lateral hypothalamic nucleus (LH) as principal sites of Ob-R expression in the central nervous system. Each of these nuclei express one or more neuropeptides and neurotransmitters such as neuropeptide Y (NPY) and melanocyte-stimulating hormone alpha (-MSH), that regulate food intake and/or body weight, probably by actions downstream of leptin (Friedman JM and Halaas JL, 1998; Flier JS and Maratos-Flier E, 1998).

Leptin and human obesity

The role of leptin in the pathogenesis of obesity may be inferred by measurement of plasma leptin. An increase in plasma leptin suggests that obesity is the result of resistance to leptin. A low or normal plasma concentration of leptin suggests that obesity is due to decreased production of leptin. This interpretation is

similar to that used in studies of insulin and the pathogenesis of type I and type II diabetes. As is the case with insulin and its receptor in diabetes, mutations of leptin and its receptor are rare in human obesity, and most obese individuals have higher levels of leptin than do non-obese individuals, an indication of leptin resistance (Flier JS, 1997).

Many genes involved in development of obesity have recently been found and most of them seem to act downstream of leptin at the hypothalamic level. Other genes involved in obesity are neuropeptides that encode leukocyte adhesion receptors, which are important cell-cell adhesion molecules in inflammatory and immune systems (Dong ZM et al., 1997), and neurocytokines like the ciliary neurotrophic factor, which receptor subunits share sequence similarity with the leptin receptor (Gloaguen I et al.., 1997). The identification of anti-obesity mechanisms that act independently or together with the leptin system may help to develop strategies for the treatment of obesity associated with leptin resistance.

Leptin has immuno-regulatory activity

Exogenous leptin up-regulates both phagocytosis and the macrophage production of proinflammatory cytokines such as tumor necrosis factor (TNF-) and interleukin-6 (Loffreda S et al.., 1998). It has been suggested that the of up-regulation of inflammatory immune responses by leptin, may contribute to several of the major complications of obesity such as increased incidence of infection, diabetes and cardiovascular disease (Loffreda S et al.., 1998; McCarty MF, 1999). This hypothesis is attractive since it would implicate a common pathogenic mechanism (lack of leptin action) for both obesity and some of its major complications. However, an alternative possibility is that regulatory mechanisms usually connected to e.g. immune functions also are of importance for the regulation of body fat.

Interleukin-6

The cytokines act as hormonal regulators of the immune system and in the body's reactions during trauma and inflammation. The cytokine interleukin-6 (IL-6) is known to be important in the development of B-lymphocytes and in the change of plasma protein production of the liver during trauma and inflammation, the so-called acute phase response. In line with this, IL-6 levels are markedly increased during acute phase response. It has been shown that IL-6-type cytokine receptors share functional specificity with the long form of the leptin receptor (Baumann H et *al.*, 1996). The role of the cytokines including IL-6 in healthy animals and humans is not well known and they are suggested to have little effect, partly because circulating levels often are low in the absence of illness (Hirano T, 1998).

Interleukin-6 and obesity

It has recently been discovered that knockout of the IL-6 gene in mice surprisingly induces "middle age onset" obesity (Wallenius V and Jansson JO, unpublished results). There is little data in the literature indicating that IL-6 has any effect on metabolic parameters in the absence of acute phase reaction and inflammation. However, there are recent reports indicating that IL-6 is released from normal adipose tissue in humans (Mohamed-Ali V *et al.*., 1997, see Fig. 1). In addition, it is well known that IL-6 is released from immune cells including macrophages, as well as endothelial cells and various other cell types (Hirano T, 1998). Moreover, both IL-6 and IL-6 receptors have been found in hypothalamic nuclei known to be important in the regulation of food intake and body weight (Schöbitz B *et al.*. 1993, see Fig. 1). These observations have drawn our attention to IL-6's potential role in the regulation of body weight.

Brief description of the drawings:

Below reference is made to the appended drawings, which illustrate the following:

Fig. 1 Possible sources of IL-6 that could be of importance for body composition and leptin sensitivity.

Fig. 2 Body weight in 15 month-old wild-type (n = 9) and IL-6 knockout (IL-$6^{-/-}$, n = 10) male mice. Values are indicated as mean ± SEM. ** P<0.01 vs. wild-type, independent t test.

Fig. 3 Plasma leptin levels in young (4 months) and old (12 months) wild-type and IL-6 knockout (IL-$6^{-/-}$) male mice. Young wild-type n = 5, Young IL-$6^{-/-}$ n = 3, Old wild-type and IL-$6^{-/-}$ n = 5. Values are indicated as mean ± SEM. # P<0.05, ## P<0.01 vs. corresponding young animals, independent t test. * P<0.05 vs. young wild-type, independent t test.

Fig. 4 Effect of vehicle and leptin administration on food intake in 15 month-old wild-type and IL-6 knockout (IL-$6^{-/-}$) male mice. (a) Vehicle treated mice, wild-type n = 5, IL-$6^{-/-}$ n = 4. (b) Leptin at 120 µg/day, n = 5 per genotype. (c) Leptin at 240 µg/day, wild-type n = 5, IL-$6^{-/-}$ n = 3. Thick black bars represent leptin treatment period. Vehicle or leptin was injected intraperitoneally twice daily. Values are indicated as mean ± SEM. # P<0.05, ## P<0.01, ### P<0.001 vs. study day 0, paired t test with the Bonferroni correction. * P<0.05, ** P<0.01 vs. wild-type, independent t test.

Fig. 5 Effect of vehicle and leptin administration on body weight in 15 month-old wild-type and IL-6 knockout (IL-$6^{-/-}$) male mice. (a) Vehicle treated mice, wild-type n = 5, IL-$6^{-/-}$ n = 4. (b) Leptin at 120 µg/day, n = 5 per genotype. (c) Leptin at 240 µg/day, wild-type n = 5, IL-$6^{-/-}$ n = 3. Thick black bars represent leptin treatment period. Vehicle or leptin was injected intraperitoneally twice daily. Values are indicated as mean ± SEM. # P<0.05, ## P<0.01, ### P<0.001 vs. study day 0, paired

t test with the Bonferroni correction. $P<0.05$, ** $P<0.01$, *** $P<0.001$ vs. wild-type, independent t test.

Study objectives

In the present study we investigated whether endogenous IL-6 may act as a cofactor for leptin by influencing leptin responsiveness in mice. We measured plasma leptin levels in male IL-6 knockout (IL-$6^{-/-}$) and wild-type mice and then treated the mice with different doses of leptin and measured the effect of leptin treatment on food intake and body weight.

Materials and methods

Animals

IL-$6^{-/-}$ knockout mice were generated as described by Kopf *et al.* 1994. To reduce genetic heterogeneity, the IL-$6^{-/-}$ mice were backcrossed for 8 generations resulting in mice genetically consisting of a more than 99.5 % C57BL/6.

Age-matched normal C57BL/6 male mice from B&K Universal AB (Sollentuna, Sweden) were used as wild-type controls. All mice were housed separately (due to aggressiveness) in standard cages under standardised environmental conditions, *i.e.* 24-26°C, 50-60% relative humidity, artificial lightning at 05:00-19:00 hours, with water and pelleted food (Beekay Feeds, Rat and mouse standard diet, B&K Universal AB, Sollentuna, Sweden) *ad libitum*. All procedures regarding the mice were conducted in accordance with protocols approved by the institution and the local ethical committee on animal care.

Measurements of body weight and food intake

Body weight was measured using a weighing scale (A & D Instruments, EK-200G). Food consumption was measured daily by weighing the food left over 24 h after the previous fillup. Basal food intake was measured during pretreatment with saline injections before onset of the

leptin treatment. Body weight and food intake was measured for 3 days after the end of leptin treatment.

Leptin measurement

For measurement of plasma leptin, tail blood samples were collected from young (4 months) and old (12 months) wild-type and IL-6 $^{-/-}$ male mice. Plasma leptin was determined with a recently described radioimmunoassay (Ahrén *et al.*,1997; Linco Research, St Charles, Mo, USA). The method uses a polyclonal rabbit antibody raised against recombinant mouse leptin, ^{125}I-labeled tracer prepared with recombinant mouse leptin and mouse leptin as standard. Rabbit antirabbit IgG was used for separation of bound and free leptin.

Leptin treatment

15-month-old IL-6 $^{-/-}$ and wild-type males received intraperitoneal (ip) injections of leptin at doses of 120 µg/day or 240 µg/day or vehicle twice daily (at 08:30 and 17:00) for 3 consecutive days. Human leptin was obtained from PeproTech (Rocky Hill, NJ, USA) and dissolved in sterile PBS, 0.1% BSA. In order to get the animals used to injections, mice were given saline injections twice daily before the start of the leptin treatment.

Statistical analysis

The descriptive statistical results are presented as means ± SEM. Independent t test was used to test between-group differences. Within-group differences were analysed using paired *t* test followed by the Bonferroni correction. $P < 0.05$ was considered significant.

Results

Body weight of IL-6 $^{-/-}$ and wild-type mice

The body weights of 15 month-old IL-6 $^{-/-}$ male mice were increased by 17% compared to wild-type male mice (Fig. 2).

Plasma leptin levels in young and old IL-6 $^{-/-}$ and wild-type mice

The results of a preliminary measurement showed no difference in plasma leptin levels between old IL-6 $^{-/-}$ and wild-type male mice (Fig. 3). Young IL-6 $^{-/-}$ male mice exhibited decreased plasma leptin levels compared to young wild-type male mice. Plasma leptin levels in both old wild-type and IL-6 $^{-/-}$ male mice were increased compared to the corresponding younger mice (Fig. 3).

Effects of leptin treatment on food intake

Vehicle treatment (PBS, 0.1% BSA) showed no effect on food intake compared to baseline levels in wild-type and IL-6 $^{-/-}$ mice (Fig. 4a).

In contrast, treatment with leptin at a dose of 120 µg / day to wild-type male mice led to a 40% decrease in food intake during the first two treatment days compared to baseline levels (baseline level: 4.91 ± 0.08 g). Food intake was not significantly decreased in IL-6 $^{-/-}$ mice during treatment with leptin in this dose (Fig. 4b). The decrease in food intake was significantly larger in wild-type mice than in IL-6 $^{-/-}$ mice on day 1-3 of leptin treatment (Fig. 4b). At the end of the leptin treatment, food intake was normalised within 2 days in wild-type mice.

Leptin treatment at a larger dose (240 µg / day) led to a reduction of food intake in wild-type males with the largest decrease (50%) from baseline level during the third treatment day (baseline level: 4.46 ± 0.30 g, Fig. 4c). There was no decrease in food intake in the IL-6 $^{-/-}$ mice (Fig. 4c). Three days after the end of the leptin treatment, food intake increased significantly to above baseline levels in wild-type mice and there was a similar tendency in IL-6 $^{-/-}$ mice (Fig. 4c).

Effects of leptin treatment on body weight

Vehicle treatment (PBS, 0.1% BSA) showed no effect on body weight compared to baseline levels in wild-type and IL-6 $^{-/-}$ mice (Fig. 5a).

However, body weights were markedly reduced during and after leptin treatment (120 µg / day) in wild-type mice, while the effect was less pronounced in the IL-6 $^{-/-}$ mice (Fig. 5b). The reduction in body weight was significantly larger in wild-type mice than IL-6 $^{-/-}$ mice day 1-4 after initiation of leptin treatment.

Body weights were significantly reduced in wild-type mice both for three days during and for three days after a higher dose of leptin treatment (240 µg / day, Fig. 5c). There was a tendency towards decreased body weights in leptin treated IL-6 $^{-/-}$ mice, but this decrease was not significant tested with paired *t* test followed by the Bonferroni correction for five comparisons. On day 3 of leptin treatment, the decrease in body weight was significantly smaller in IL-6 $^{-/-}$ mice than in wild-type mice.

Discussion

IL-6 and leptin responsiveness

In this study we show that IL-6 $^{-/-}$ mice have decreased responsiveness to leptin treatment compared to wild type mice. These findings indicate that presence of endogenous IL-6 is of importance for normal leptin responsiveness. Leptin treatment induced a significant reduction in food intake in the wild-type mice, but not in the IL-6 $^{-/-}$ mice. In addition, the suppressive effect of leptin on body weight was less pronounced in IL-6 $^{-/-}$ mice than in wild-type mice. These effects of IL-6 may be related to the IL-6 receptor structure, since it has been shown that IL-6 type cytokine receptors share functional specificity with the long form of the leptin receptors (Ob-Rb, Baumann H *et al.*, 1996). The receptor subunits for ciliary neurotrophic factor (CNTF) have been shown to

share sequence similarities with Ob-Rb, Gloaguen I et al., 1997) and IL-6 receptors. When administered systemically, CNTF can reverse obesity in various animal models, including *db* mice lacking leptin receptors (Gloaguen I *et al.*, 1997). All three of these systems, leptin, IL-6 and CNTF, signals through the JAK-STAT pathway to regulate gene expression (Flier JS, 1997; Hirano T, 1998; Gloaguen I *et al.*, 1997). Cross-reactivity between the three systems at the receptor or post-receptor level may serve as an explanation for the link between regulation of body weight by leptin and IL-6 (as well as CNTF).

IL-6 and body weight

The body weights of the IL-6 $^{-/-}$ mice in this study were significantly higher compared with the body weights of wild-type mice. This result is supported by the recent finding that IL-6 $^{-/-}$ mice develop "middle age onset" obesity (Wallenius V and Jansson JO, unpublished results). There may be several possible reasons why the obese phenotype of these mice has not been noticed previously. IL-6 $^{-/-}$ mice are commonly used to investigate the role of IL-6 in various infectious and inflammatory models (Kopf *et al.* 1994), but the weight gain in the IL-6 $^{-/-}$ mice was not observed until they were "middle aged", that is about 4 months of age. Younger animals are preferred for studying infection and inflammation. Moreover, the IL-6 $^{-/-}$ mice in this study were back-crossed for 8 generations to a 99.5% pure C57BL/6 background, which may be of importance for the development of the obese phenotype. If so, this raises the question whether the obese phenotype is exclusive for IL-6 $^{-/-}$ mice with a C57BL/6 background or if it also would be seen in other mice strains deficient for IL-6.

The weight gain in the IL-6 $^{-/-}$ mice could be secondary to the development of leptin resistance indicated by this study. If this is the case, one could expect the IL-6 $^{-/-}$ mice to have a higher level of basal food intake

compared to wild-type mice. So far, studies on basal food intake in IL-6 $^{-/-}$ mice have not shown such results. There are also indications in the literature, suggesting that IL-6 affects energy expenditure rather than feeding (Chrousos GP, 1995). If IL-6 acts mainly on the regulation of energy expenditure relative to the regulation of appetite/food intake, the finding in this study that endogenous IL-6 may potentiate the suppressive effect of leptin on food intake is a bit surprising (Friedman JM and Halaas JL, 1998). It is common knowledge that food intake and appetite is reduced during infectious diseases and inflammation, conditions which are associated with increased levels of circulating IL-6 (Hirano T, 1998). However, there have been few earlier indications that the low basal production of IL-6 in healthy animals would affect food intake or fat mass. So far, the reason for the weight gain in the IL-6 $^{-/-}$ mice is not clear and needs further investigation.

Immune function and body weight

The possible new role for IL-6 in the regulation of body weight suggested by the findings in IL-6 knockout mice is in line with other findings, including that regulatory mechanisms usually connected to immune functions also are of importance for the regulation of body weight. Genes involved in obesity include leukocyte adhesion receptors, which are important cell-cell adhesion molecules in inflammatory and immune systems (Dong ZM *et al.*, 1997). Moreover, the body weight regulating protein mahogany has been shown to be identical to a membrane bound form of attractin, a protein with immune function released from activated T-cells (Gunn TM *et al.*, 1999). Finally, leptin is known to stimulate immune functions, especially as seen in starved animals (Loffreda S *et al.*; Friedman JM and Halaas JL, 1998).

Plasma leptin levels in IL-6 $^{-/-}$ mice

Measurement of plasma leptin levels in male IL-6 $^{-/-}$ mice and wild-type male mice showed no significant difference between old IL-6 $^{-/-}$ mice and old wild-type mice. This is surprising for two reasons. Firstly, the IL-6 $^{-/-}$ mice were heavier than the wild-type mice because of increased body fat mass (Wallenius V and Jansson JO, unpublished results). Since plasma leptin levels are highly correlated with adipose tissue mass (Friedman JM and Halaas JL, 1998), the plasma leptin levels of the IL-6 $^{-/-}$ mice were expected to be higher than in the wild-type mice. Secondly, leptin resistance in the IL-6 $^{-/-}$ mice, as indicated by this study, is associated with increased plasma leptin levels. For instance, elevation of plasma leptin is seen in most obese humans with leptin resistance (Flier JS and Foster DW, Williams textbook of endocrinology 9th edition). Other measurements of plasma leptin levels in female mice have shown increased levels in the IL-6 $^{-/-}$ mice compared to wild-type mice (Wallenius V and Jansson JO, unpublished results). It is known that the levels of circulating leptin are higher in females than in males (Flier JS and Foster DW, Williams textbook of endocrinology 9th edition), and there are several gender differences in the regulation of fat mass (Vettor R et al., 1997). Therefore, the preliminary results of the measurements of plasma leptin levels in male IL-6 $^{-/-}$ mice need to be repeated and investigated further.

Study limitations

The leptin treatment of the IL-6 $^{-/-}$ and wild-type mice was in this study performed on male mice. To further investigate the importance of IL-6 in leptin responsiveness, similar measurements of the effect of leptin treatment on food intake and body weight may be performed in female IL-6 $^{-/-}$ and wild-type mice. Especially considering the gender differences discussed above.

Conclusion and future perspectives

Our study suggests that the presence of endogenous IL-6 is of importance for normal leptin responsiveness. An interesting next step could now be to co-treat IL-6 $^{-/-}$ and wild-type mice with leptin and IL-6. If the outcome of such a study would show a normal response to leptin (decrease in food intake and body weight) in IL-6 treated IL-6 $^{-/-}$ mice, this would support that IL-6 is important for normal leptin responsiveness. It would also be of interest to investigate if low levels of IL-6 are associated with leptin resistance in obese humans. If so, IL-6 could be an effective treatment of obesity in humans with leptin resistance.

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CLAIMS

1. Use of a first substance that upon administration to a patient will lead to an increased level of an interleukin-6 (IL-6) receptor agonist in combination with a second substance that will intensify the effect of said agonist for the production of a medicinal product for treatment of obesity and/or disturbances of blood fats, characterised in that said second substance is leptin.

2. Use according to claim 1, wherein said first substance is an IL-6 receptor agonist.

3. Use according to claim 2, wherein said first substance is IL-6.

4. Use according to any one of the claims 1-3, wherein said obesity and/or disturbances of blood fats is caused by a pathological disturbance of fat metabolism.

5. Use according to claim 4, wherein said obesity is mainly visceral or intraabdominal.

6. Use according to any one of the claims 1-5, wherein said obesity is observed despite high levels of circulating leptin.

7. Use according to any one of the claims 1-6, wherein said obesity is accompanied by leptin insensitivity.

8. Use according to any one of the claims 1-3, wherein said obesity and/or disturbances of blood fats is caused by a pathological disturbance of blood fats.

9. Use according to claim 8, wherein said condition is a pathological increase of serum triglycerides.

10. Use according to claim 8, wherein said condition is a pathological increase of serum cholesterol.

11. Use according to any one of the claims 1-10, wherein said medicinal product is suitable for treatment of a cardiovascular disease.

12. Use according to any one of the claims 1-11, wherein said medicinal product is suitable for treatment of a condition due to ageing.

13. Use according to claim 12, intended for a human patient of the age 30 years or older.

14. A method for treatment of obesity and/or disturbances of blood fats wherein a pharmaceutically effective amount of a first substance that upon administration to a patient will lead to an increased level of an interleukin-6 (IL-6) receptor agonist in combination with a second substance that will intensify the effect of said agonist is administered to said patient.

15. A method according to claim 14, wherein said substance is an IL-6 receptor agonist.

16. A method according to claim 15, wherein said substance is IL-6.

17. A method according to any one of the claims 14-16, wherein said obesity and/or disturbances of blood fats is caused by a pathological disturbance of fat metabolism.

18. A method according to claim 17, wherein said obesity is mainly visceral or intraabdominal.

19. A method according to according to any one of the claims 14-18, wherein said obesity is observed despite high levels of circulating leptin.

20. A method according to according to any one of the claims 14-19, wherein said obesity is accompanied by leptin insensitivity.

21. A method according to any one of the claims 14-16, wherein said obesity and/or disturbances of blood fats is caused by a pathological disturbance of blood fats.

22. A method according to claim 21, wherein said condition is a pathological increase of serum triglycerides.

23. A method according to claim 21, wherein said condition is a pathological increase of serum cholesterol.

24. A method according to any one of the claims 14-23, wherein said medicinal product is suitable for treatment of a cardiovascular disease.

25. A method according to any one of the claims 14-24, wherein said medicinal product is suitable for treatment of a condition due to ageing.

26. A method according to claim 25, wherein said patient is a human of the age 30 years or older.

ABSTRACT

Use of a first substance that upon administration to a patient will lead to an increased level of an interleukin-6 agonist in combination with a second substance that will intensify the effect of said agonist for the production of a pharmaceutical composition for treatment of obesity and/or disturbances of blood fats, wherein said factor is leptin is disclosed.

Also a method for treatment of obesity and/or disturbances of blood fats wherein a pharmaceutically effective amount of a first substance that upon administration to a patient will lead to an increased level of an interleukin-6 agonist is administered together with a second substance that will intensify the effect of said agonist is disclosed.

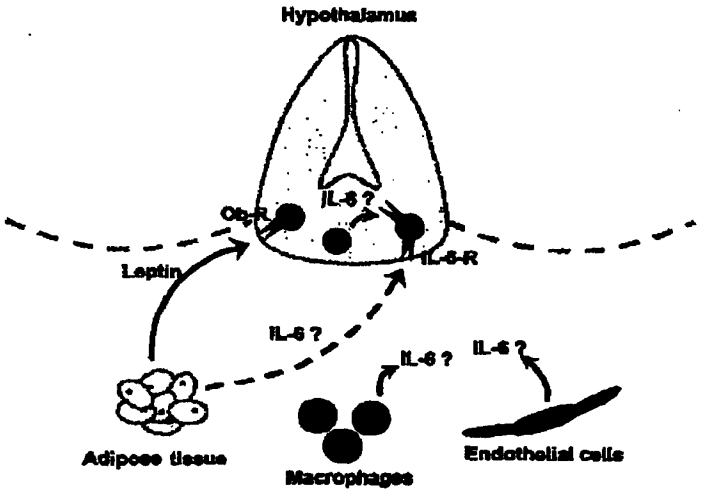

Fig. 1

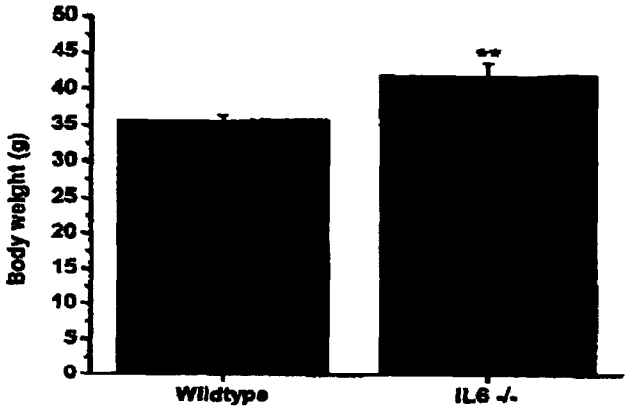

Fig. 2

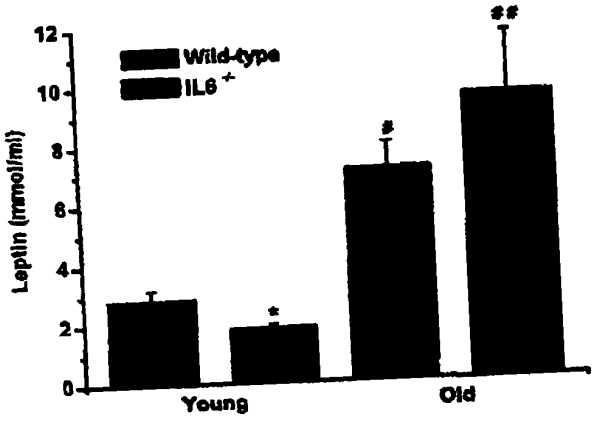

Fig. 3

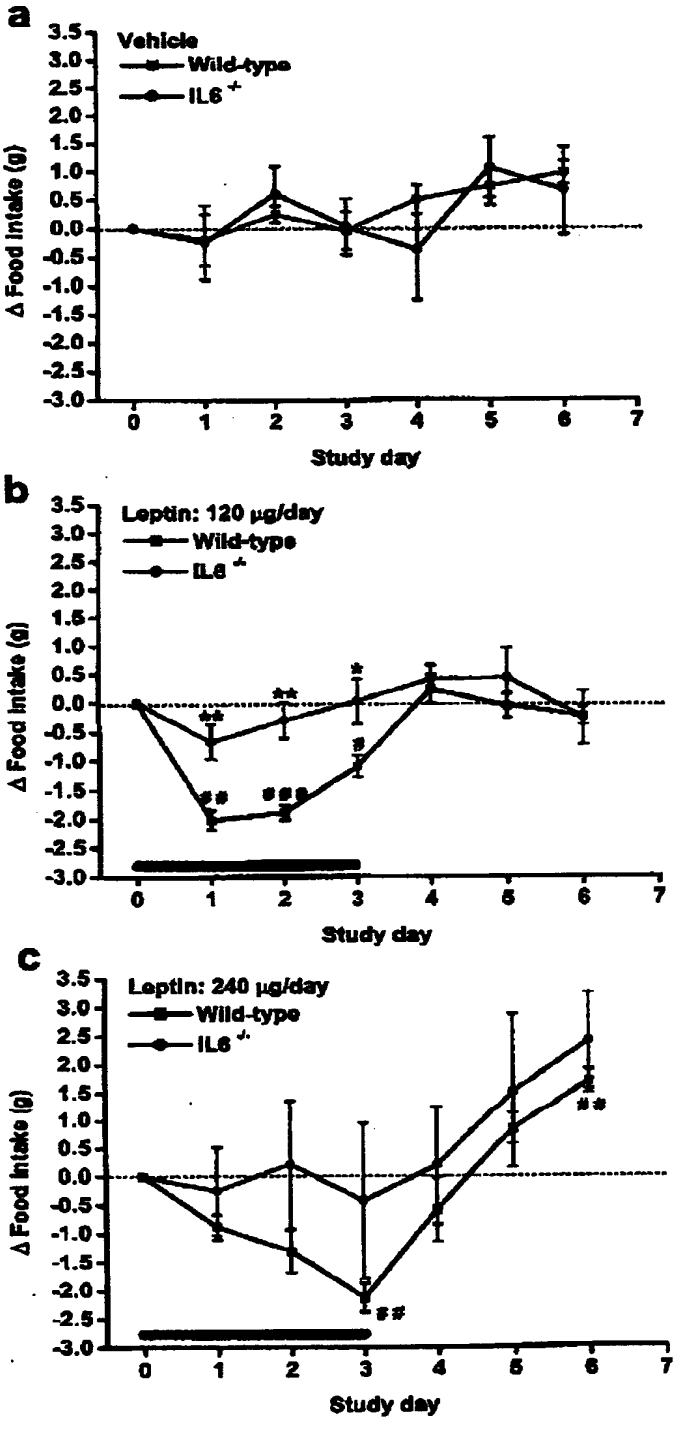

Fig. 4

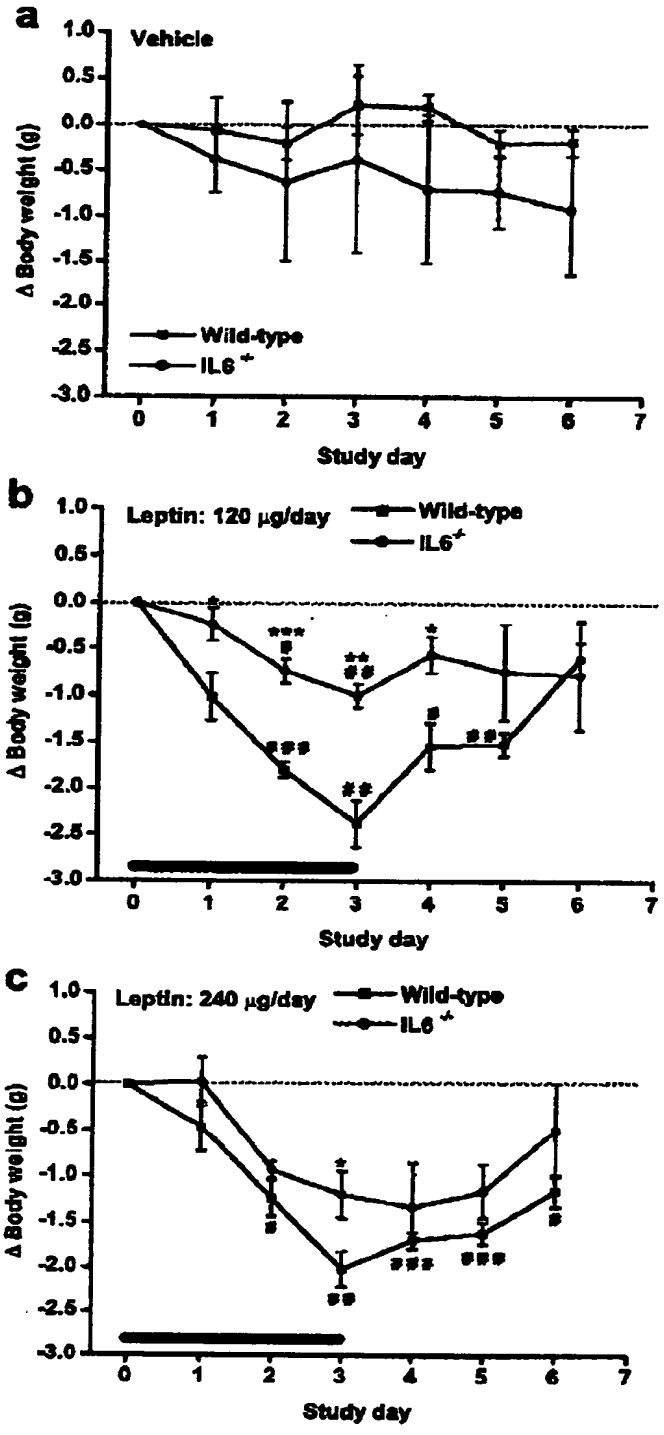

Fig. 5